

Editorial Comment

Tell Me What Ails You, and I'll Tell You Why It's Your Fault*

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Several years ago, I saw a cartoon by Glasbergen of a girl talking to a young boy. The caption read, "Let's play doctor. I'll give you a list of my ailments, and you blame it all on my hormones." To me, this cartoon epitomizes one side of the ongoing debate as to whether women patients are appropriately and fairly treated for their medical symptoms and signs of disease. In cardiology, this debate focuses on the question of whether women with symptoms of coronary artery disease receive the same intensity of diagnostic testing and treatment as do men. This question stimulates strong emotional responses in cardiologists and epidemiologists (1).

Coronary Artery Survival Study registry study. The Coronary Artery Survival Study (CASS) registry study by Davis et al. (2) in this issue of the Journal appears to side with those who suggest that such bias in the treatment of women with coronary artery disease does not occur. The CASS registry study analyzed rates of coronary artery bypass surgery and long-term survival in ~15,000 men and women who had operable coronary artery disease at the time of their initial coronary angiography. Women in the study were, on average, 3 years older and had higher rates of diabetes and symptomatic congestive heart failure and angina than study men. However, the men had more extensive coronary artery disease and poorer left ventricular contraction scores than the women. The rate at which coronary artery bypass surgery was performed in the women compared with that in the men was not different, and there were few differences in the long-term survival of the men and women. These results appear to suggest that physicians offered surgical therapy to women patients with operable coronary artery disease on the basis of their symptoms, coronary anatomy and left ventricular function. The decision-making process was apparently not biased by the gender of the patient (2).

These results are reassuring and suggest that once coronary angiography is performed, physicians use these objective data to make rational decisions about revascularization. Moreover, the CASS registry study is consistent with other

studies suggesting that after angiography, the utilization of coronary revascularization procedures, including coronary artery bypass surgery, is not greater in men than in women (3-6). The CASS registry study appears to present proof that if there is a bias against women in aggressively diagnosing and treating coronary artery disease, it occurs before coronary angiography. The sophisticated statistical analysis, the large number of patients in the study, the nearly complete follow-up data, the strong study design and the impressive reputations of these scientists all strengthen the conclusions of the CASS registry study.

However, I believe that the conclusions of Davis et al. (2) should be interpreted cautiously. There is strong evidence of bias in the way that we treat women with suspected coronary artery disease. This evidence is found in several disciplines of medicine and is supported by retrospective cohort studies, registries and case series from individual hospitals. Most critically, in addition to this evidence, the conclusions drawn from the CASS registry study are based on information gleaned from a highly selected group of women. Conclusions based on their management are probably not generalizable to most women with symptoms of coronary disease.

Gender bias in clinical decisions. In the field of clinical decision analysis, there is evidence that clinical decisions are influenced by a patient's gender. In fact, the cultural milieu in which the patient and physician operate may be as important as the biomedical considerations of whether a patient is offered a diagnostic test or therapy. Characteristics of the patient, the clinician, the health care system and the relationship of the clinician to the patient are all important sociologic influences in the clinical decision process. A patient's gender may be one of these important sociologic variables. Physicians may diagnose and treat women, at least in part, on the basis of gender biases learned during their medical training and careers (7).

In the field of epidemiology, there is also strong evidence that coronary artery disease is treated differently in men and women. Coronary artery disease incidence, prevalence and case fatality rates and initial presentation of symptomatic coronary artery disease certainly differ between men and women. However, these epidemiologic differences are not great. In the United States, coronary artery disease is the leading cause of death in women. The number of deaths each year from coronary artery disease is not different for men and women (8). Between the ages of 45 and 64 years, the prevalence of coronary heart disease is approximately twice as high in men. After age 65, this difference essentially disappears. Death rates from coronary artery disease tend to mirror the prevalence rates. For women and men between the ages of 45 and 64 years, the death rate from coronary artery disease is about three times higher in men than women. However, the death rate after age 65 becomes essentially the same (9,10). Angina pectoris is common in women, and whether it is diagnosed by a physician or by use of a standardized questionnaire, is prevalent in >5% of women between the ages of 40 and 60 years. This is not greatly different from the rate found

*Editorials published in *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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in men, although women in most studies have a higher rate of angina than their male counterparts (1). Clearly, the gender differential of coronary artery disease between men and women is not as great as has been previously suggested (11).

Despite this similarity between men and women in the burden of coronary artery disease, men are much more likely than women to undergo aggressive treatment for symptomatic coronary artery disease. For example, men are four to five times more likely than women to undergo coronary artery bypass surgery (3). This difference between men and women in utilization of coronary artery bypass surgery persists even after adjusting for principal diagnosis, age, heart failure, diabetes, race and insurance status. Even in the setting of an acute myocardial infarction, and with women reporting higher rates of disability from angina, women are only half as likely as men to undergo cardiac catheterization or bypass surgery. Clinical variables, including functional status, do not appear to greatly change this discrepancy (5).

Utilization of diagnostic and therapeutic procedures for coronary artery disease in men and women at individual tertiary care referral hospitals is less consistent than at multiple-site studies. Some series show that women are older and are referred for bypass surgery later in the course of their disease than men, with women likely to be referred for unstable angina, postmyocardial infarction angina or heart failure. Men, in contrast, were referred because of abnormal exercise tolerance tests (12). Other series show similar rates of utilization after acute myocardial infarction. In one large series (4), the rate of coronary artery angiography and angioplasty was not different in patients of similar ages, but women appeared less likely to undergo bypass surgery than men. In another large series (13), there was no difference in utilization of coronary artery bypass surgery, but the reasons why women were offered bypass surgery differed from those in men. Women in the lowest risk group, those least likely to benefit from operation, were offered bypass surgery less frequently than their male counterparts in the same risk group. In the highest risk group, the group most likely to benefit from operation, there was no difference in rates of bypass surgery (13).

Women also appear to have a higher death rate after operation or acute myocardial infarction. For example, women are more likely to die during an acute myocardial infarction than men. In fact, male case fatality rates rarely surpass female rates after an acute coronary event (11). Early hospital mortality after coronary artery bypass surgery also appears to be higher for women than men (14-16). This excess mortality in women is probably due to multiple factors, such as the older age of the women, the higher rate of associated comorbidity or the increased acuity of women at the time of operation. However, many investigators (16) do not believe that these factors explain all the high risk of coronary artery bypass surgery. The smaller body size of women and the smaller coronary arteries, which may be less suitable for bypass grafting, are believed to explain some of this excess risk. This excess risk was reported early in the CASS study, as well as by other investigators (15).

Finally, another line of evidence supporting differential treatment of women compared with men is philosophical. The debate about utilization of procedures in coronary artery disease often uses the language of exploitation and attributes differences in outcomes between men and women back to women. Women are conceptualized as a cause of the problem. This ideologic process of unintentional and well-meaning, yet often self-serving, distortion of reality is seen in many social and public health problems (17). In the context of coronary artery disease, this language often suggests that coronary artery disease is a "man's disease," that women may have symptoms out of proportion to the extent of their coronary artery obstructions and that when women's arteries are affected, their arteries are "bad for revascularization." The context of the debate is thus put in the context of a problem with women rather than in the context of the causes of the disease itself.

Generalizability of CASS registry study. The CASS registry study addresses many of these key issues. In my opinion, it is a valid, internally consistent study that has limited generalizability. My concerns about the study are based on two lines of reasoning. First, the analysis is based on a highly selected group of women who are unlikely to be representative of most women with coronary artery disease. Second, it was not clear to me when the decision-making for coronary bypass surgery actually occurred. It may have occurred, at least in part, well before the cardiac catheterization was performed. Physicians may be less objective than suggested by the CASS registry study if they have already decided to offer an operation, provided that the test shows an operable coronary lesion.

The CASS registry was designed to serve as a repository of information on patients undergoing coronary angiography for a clinical trial of medical and surgical treatment of coronary disease (18). By no means is this registry representative of the U.S. population with coronary artery disease. Referral for cardiac catheterization is a complex process that is almost certainly influenced by clinical and nonclinical factors. The CASS registry cannot be used to test a hypothesis about selection bias in cardiac catheterization. Furthermore, if a conditional decision to refer to bypass surgery precedes cardiac catheterization, an analysis of a registry is of limited value in assessing gender bias in coronary artery disease surgery rates.

That such selection pressures occurred in the CASS registry study is suggested by the proportion of men and women within the registry. There was no age limit for entry into the registry (18), and one should not expect a great difference in the proportion of men and women in the registry. However, the difference in men and women in the registry is huge. After excluding men and women who had nonoperable coronary artery disease, only slightly <16% of the patients in the study were women. Even within the age range of most patients in the study, one would expect more women to have been entered into the registry. This ratio 5 or 6 to 1 of men to women should have been closer to the ratio of 2:1 of men to women expected within the 45- to 64-year old age group, as described previously. This ratio is also greater than the 3:1 ratio of coronary

death rates of men and women within this age group. Almost certainly, strong selection pressures contributed to determining which patients with symptomatic coronary artery disease were referred for coronary angiography.

That ~50% of the women in the registry have normal coronary arteries compared with only 20% of the men only suggests to me that there were different reasons for referring men and women for coronary angiography. These differential reasons were not homogeneous within each gender group. Some women may have been referred for advanced coronary artery disease; others may have been referred for severe, but nonspecific, chest pain. The reasons for referral to angiography for men may have been more homogeneous and may have reflected more specific symptoms. Women do not appear to have been offered cardiac catheterization for the same reasons as men.

This type of selection process, which discriminates some types of patients with coronary disease from others, does not invalidate the main results of a clinical trial. In fact, it may be the only way in which the clinical trial can proceed. However, it does limit the generalizability of the findings to the types of patients who were in the study. Questions that are particularly vulnerable to limits of generalizability are generally those that are not related to the initial hypothesis of the trial, as in this example. In general, selection procedures are often adequate to protect the original hypothesis.

Conclusions. The CASS registry study presents a sophisticated analysis of a group of women who had operable coronary artery disease defined by cardiac catheterization. At best, this study can only draw conclusions about women who reach this advanced stage of their diagnostic evaluation. No conclusion can be drawn about the selection process by which women are referred for angiography. Even for women at this stage of their diagnostic evaluation, it seems that the conclusions are not generalizable. In the important debate of whether women are discriminated against in the diagnosis and management of coronary artery disease, the CASS registry study provides some encouraging information. In a highly selected group of women, bias does not occur. However, these findings should not be extended to most women with coronary artery disease.

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